



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/415		A1	(11) International Publication Number: WO 99/61019 (43) International Publication Date: 2 December 1999 (02.12.99)
(21) International Application Number: PCT/US99/11322 (22) International Filing Date: 21 May 1999 (21.05.99) (30) Priority Data: 60/086,494 22 May 1998 (22.05.98) US		(81) Designated States: AE, AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), EE, EE (Utility model), ES, FI, FI (Utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(71) Applicant: AVANIR PHARMACEUTICALS [US/US]; 9393 Towne Centre Drive #200, San Diego, CA 92121 (US). (72) Inventors: SIRCAR, Jagadish; Avanir Pharmaceuticals, 9393 Towne Centre Drive #200, San Diego, CA 92121 (US). RICHARDS, Mark, L.; Avanir Pharmaceuticals, 9393 Towne Centre Drive #200, San Diego, CA 92121 (US). CAMPBELL, Michael, G.; Avanir Pharmaceuticals, 9393 Towne Centre Drive #200, San Diego, CA 92121 (US). MAJOR, Michael, W.; Avanir Pharmaceuticals, 9393 Towne Centre Drive #200, San Diego, CA 92121 (US). (74) Agent: ALTMAN, Daniel, E.; Knobbe, Martens, Olson & Bear, LLP, 16th floor, 620 Newport Center Drive, Newport Beach, CA 92660 (US).		Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	

(54) Title: BENZIMIDAZOLE DERIVATIVES AS MODULATORS OF IgE

(57) Abstract

This invention relates to a family of diacyl benzimidazole analogs, which are inhibitors of the IgE response to allergens. These compounds are useful in the treatment of allergy and/or asthma or any diseases where IgE is pathogenic.

BENZIMIDAZOLE DERIVATIVES AS MODULATORS OF IgE

Background of the Invention

This invention relates to small molecule inhibitors of the IgE response to allergens that are useful in the treatment of allergy and/or asthma or any diseases where IgE is pathogenic.

An estimated 10 million persons in the United States have asthma, about 5% of the population. The estimated cost of asthma in the United States exceeds \$6 billion. About 25% of patients with asthma who seek emergency care require hospitalization, and the largest single direct medical expenditure for asthma has been inpatient hospital services (emergency care), at a cost of greater than \$1.6 billion. The cost for prescription medications, which increased 54% between 1985 and 1990, was close behind at \$1.1 billion (Kelly, *Pharmacotherapy* 12:13S-21S (1997)).

According to the National Ambulatory Medical Care Survey, asthma accounts for 1% of all ambulatory care visits, and the disease continues to be a significant cause of missed school days in children. Despite improved understanding of the disease process and better drugs, asthma morbidity and mortality continue to rise in this country and worldwide (U.S. Department of Health and Human Services; 1991, publication no. 91-3042). Thus, asthma constitutes a significant public health problem.

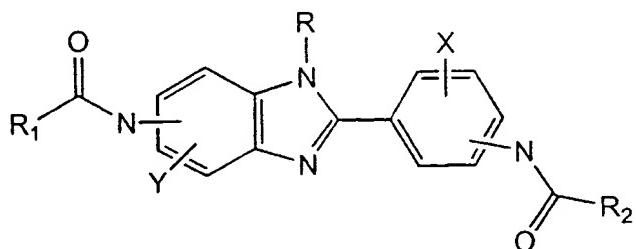
The pathophysiologic processes that attend the onset of an asthmatic episode can be broken down into essentially two phases, both marked by bronchoconstriction, that causes wheezing, chest tightness, and dyspnea. The first, early phase asthmatic response is triggered by allergens, irritants, or exercise. Allergens cross-link immunoglobulin E (IgE) molecules bound to receptors on mast cells, causing them to release a number of pre-formed inflammatory mediators, including histamine. Additional triggers include the osmotic changes in airway tissues following exercise or the inhalation of cold, dry air. The second, late phase response that follows is characterized by infiltration of activated eosinophils and other inflammatory cells into airway tissues, epithelial desquamation, and by the presence of highly viscous mucus within the airways. The damage caused by this inflammatory response leaves the airways "primed" or sensitized, such that smaller triggers are required to elicit subsequent asthma symptoms.

A number of drugs are available for the palliative treatment of asthma; however, their efficacies vary markedly. Short-acting β_2 -adrenergic agonists, terbutaline and albuterol, long the mainstay of asthma treatment, act primarily during the early phase as bronchodilators. The newer

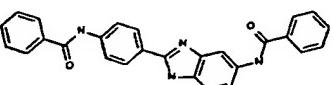
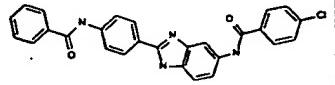
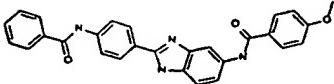
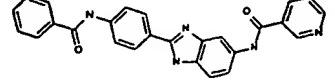
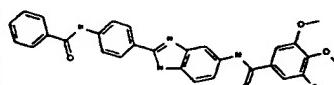
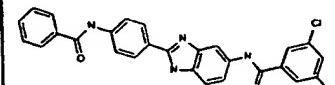
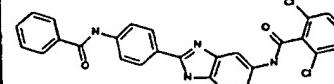
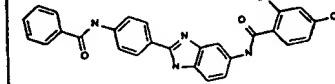
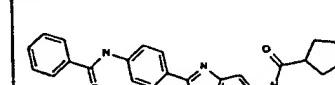
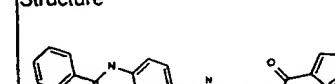
None of the current therapies eliminate the excess circulating IgE. The hypothesis that lowering plasma IgE may reduce the allergic response, was confirmed by recent clinical results with chimeric anti-IgE antibody, CGP-51901, and recombinant humanized monoclonal antibody, rhuMAB-E25. Indeed, three companies, Tanox Biosystems, Inc., Genentech Inc. and Novartis AG are collaborating in the development of a humanized anti-IgE antibody (BioWorld® Today, February 26, 1997, p. 2) which will treat allergy and asthma by neutralizing excess IgE. Tanox has already successfully tested the anti-IgE antibody, CGP-51901, which reduced the severity and duration of nasal symptoms of allergic rhinitis in a 155-patient Phase II trial (Scrip #2080, Nov 24, 1995, p.26). Genentech recently disclosed positive results from a 536 patient phase-II/III trials of its recombinant humanized monoclonal antibody, rhuMAB-E25 (BioWorld® Today, November 10, 1998, p. 1). The antibody, rhuMAB-E25, administered by injection (highest dose 300 mg every 2 to 4 weeks as needed) provided a 50% reduction in the number of days a patient required additional "rescue" medicines (antihistamines and decongestants), compared to placebo. An NDA filing for this product is projected to be in the year 2000. The positive results from anti-IgE antibody trials suggest that therapeutic strategies aimed at IgE down-regulation may be effective.

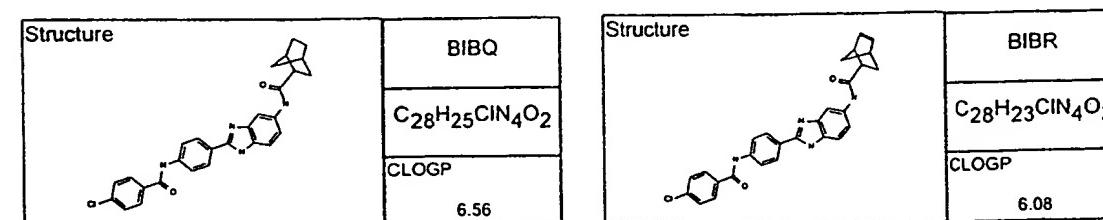
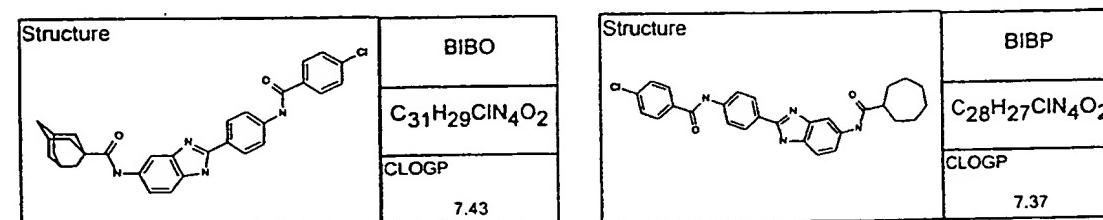
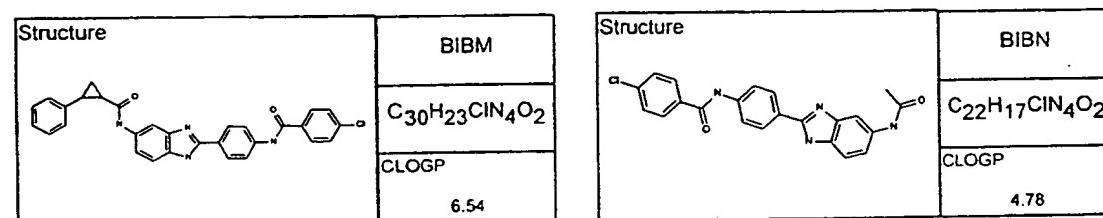
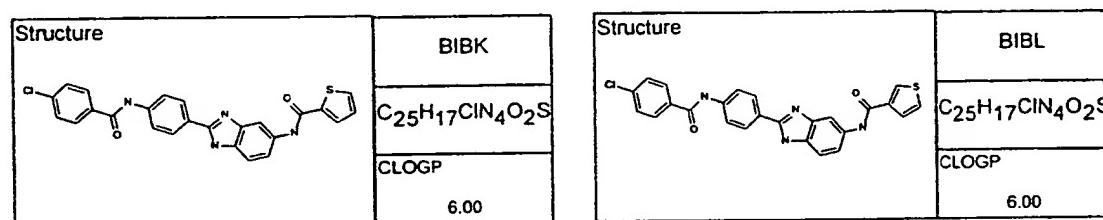
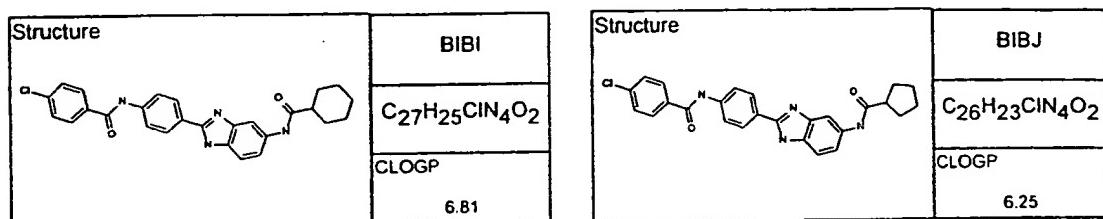
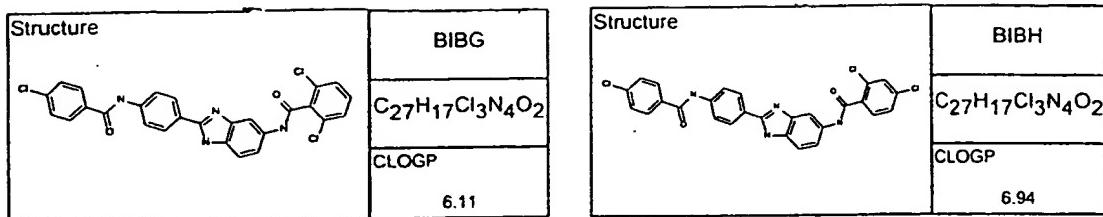
Summary of the Invention

The present invention discloses a family of related compounds for use in the treatment of a condition associated with an excess IgE level. The benzimidazole inhibitors of IgE in accordance with the present invention are represented by the generic formula:

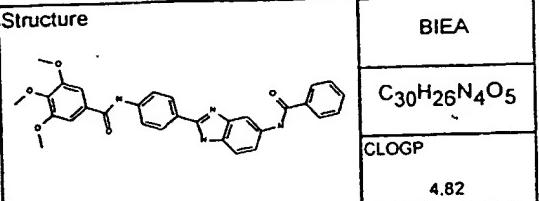
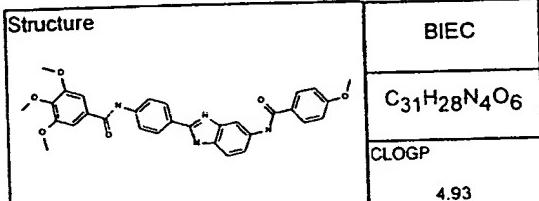
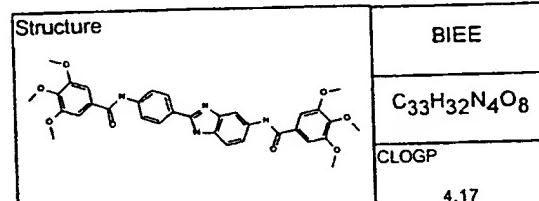
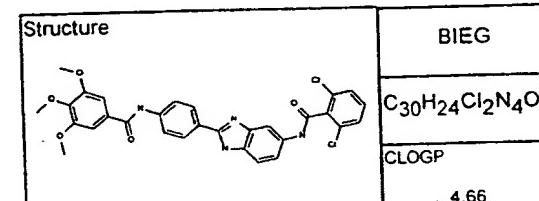
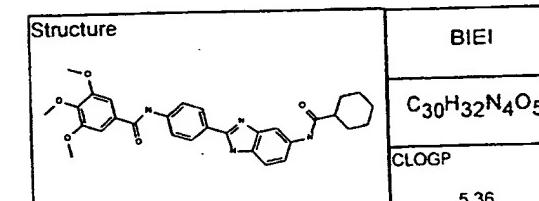
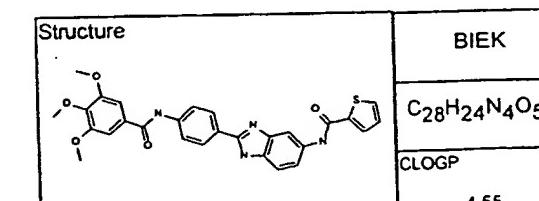


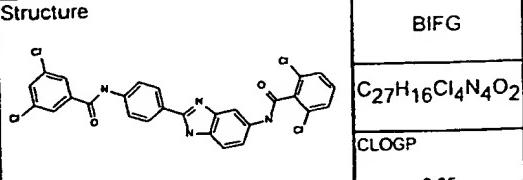
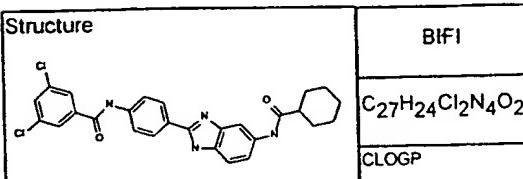
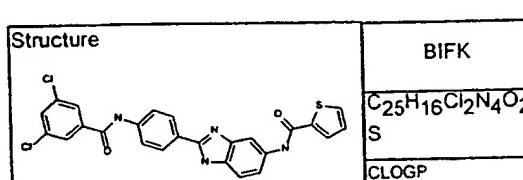
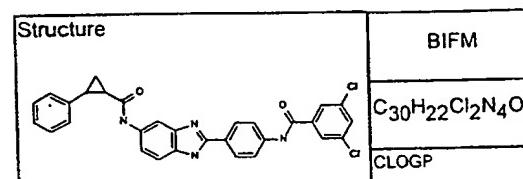
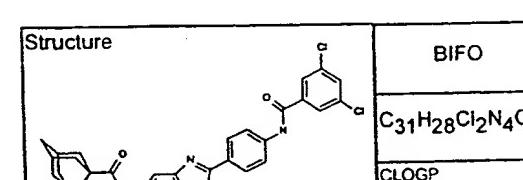
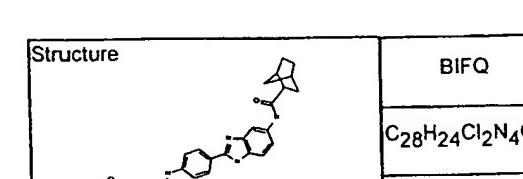
X and Y are independently selected from the group consisting of H, alkyl, alkoxy, aryl, substituted aryl, hydroxy, halogen, amino, alkylamino, nitro, cyano, CF₃, OCF₃, CONH₂, CONHR and NHCOR₁. R is selected from the group consisting of H, CH₃, C₂H₅, C₃H₇, C₄H₉,

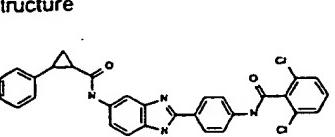
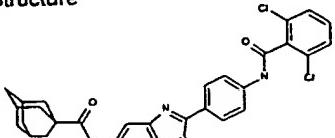
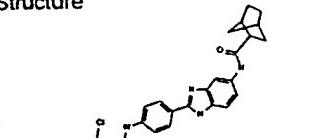
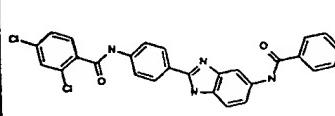
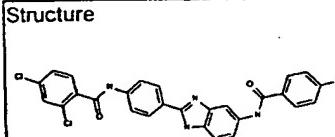
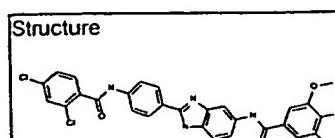
Structure	BIAA	
	<chem>C27H20N4O2</chem>	
	CLOGP	
	5.47	
Structure	BIAB	
	<chem>C27H19ClN4O2</chem>	
	CLOGP	
	6.24	
Structure	BIAC	
	<chem>C28H22N4O3</chem>	
	CLOGP	
	5.58	
Structure	BIAD	
	<chem>C26H19N5O2</chem>	
	CLOGP	
	4.28	
Structure	BIAE	
	<chem>C30H26N4O5</chem>	
	CLOGP	
	4.82	
Structure	BIAF	
	<chem>C27H18Cl2N4O2</chem>	
	CLOGP	
	6.97	
Structure	BIAG	
	<chem>C27H18Cl2N4O2</chem>	
	CLOGP	
	5.31	
Structure	BIAH	
	<chem>C27H18Cl2N4O2</chem>	
	CLOGP	
	6.14	
Structure	BIAI	
	<chem>C27H26N4O2</chem>	
	CLOGP	
	6.01	
Structure	BIAJ	
	<chem>C26H24N4O2</chem>	
	CLOGP	
	5.45	
Structure	BIAK	
	<chem>C25H18N4O2S</chem>	
	CLOGP	
	5.20	
Structure	BIAL	
	<chem>C25H18N4O2S</chem>	
	CLOGP	
	5.20	



Structure	BICM	
	<chem>C31H26N4O3</chem>	
CLOGP	5.85	
Structure	BICN	
	<chem>C23H20N4O3</chem>	
CLOGP	4.09	
Structure	BICO	
	<chem>C32H32N4O3</chem>	
CLOGP	6.75	
Structure	BICP	
	<chem>C29H30N4O3</chem>	
CLOGP	6.68	
Structure	BICQ	
	<chem>C29H28N4O3</chem>	
CLOGP	5.88	
Structure	BICR	
	<chem>C29H26N4O3</chem>	
CLOGP	5.39	
Structure	BIDA	
	<chem>C26H19N5O2</chem>	
CLOGP	4.60	
Structure	BIDB	
	<chem>C26H18ClN5O2</chem>	
CLOGP	5.37	
Structure	BIDC	
	<chem>C27H21N5O3</chem>	
CLOGP	4.71	
Structure	BIDD	
	<chem>C25H18N6O2</chem>	
CLOGP	3.41	
Structure	BIDE	
	<chem>C29H25N5O5</chem>	
CLOGP	3.95	
Structure	BIDF	
	<chem>C26H17Cl2N5O2</chem>	
CLOGP	6.10	

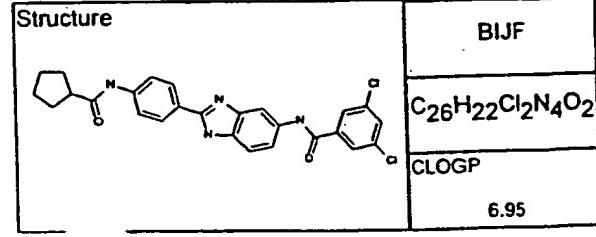
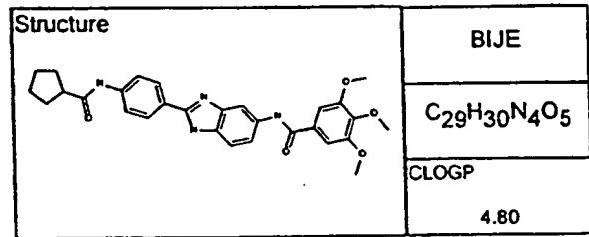
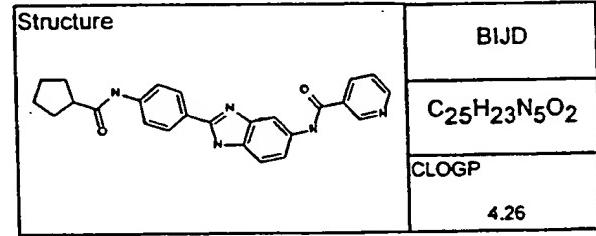
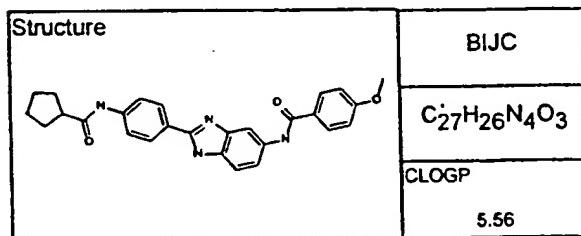
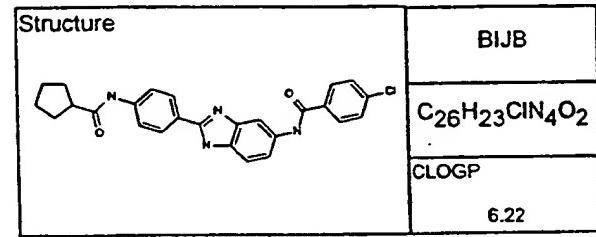
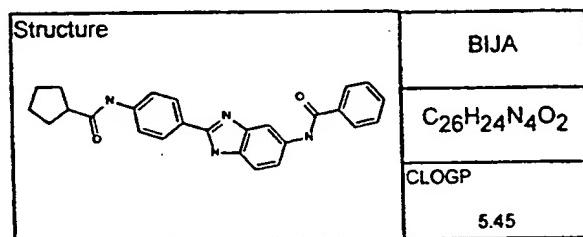
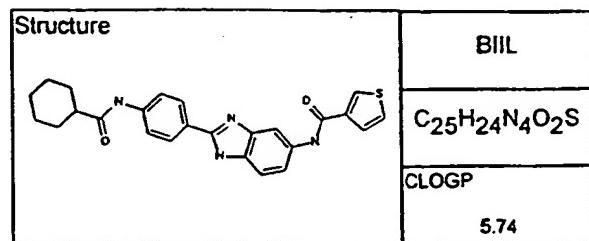
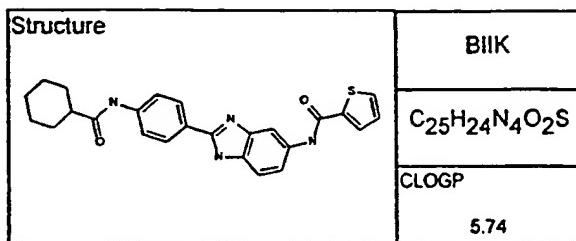
Structure	BIEA	BIEB
	<chem>C30H26N4O5</chem>	<chem>C30H25ClN4O5</chem>
	CLOGP	CLOGP
	4.82	5.59
Structure	BIEC	BIED
	<chem>C31H28N4O6</chem>	<chem>C29H25N5O5</chem>
	CLOGP	CLOGP
	4.93	3.63
Structure	BIEE	BIEF
	<chem>C33H32N4O8</chem>	<chem>C30H24Cl2N4O5</chem>
	CLOGP	CLOGP
	4.17	6.32
Structure	BIEG	BIEH
	<chem>C30H24Cl2N4O5</chem>	<chem>C30H24Cl2N4O5</chem>
	CLOGP	CLOGP
	4.66	5.49
Structure	BIEI	BIEJ
	<chem>C30H32N4O5</chem>	<chem>C29H30N4O5</chem>
	CLOGP	CLOGP
	5.36	4.80
Structure	BIEK	BIEL
	<chem>C28H24N4O5S</chem>	<chem>C28H24N4O5S</chem>
	CLOGP	CLOGP
	4.55	4.55

Structure	BIFG	BIFH
	<chem>C27H16Cl4N4O2</chem>	<chem>C27H16Cl4N4O2</chem>
	CLOGP	CLOGP
	6.85	7.68
Structure	BIFI	BIFJ
	<chem>C27H24Cl2N4O2</chem>	<chem>C26H22Cl2N4O2</chem>
	CLOGP	CLOGP
	7.54	6.99
Structure	BIFK	BIFL
	<chem>C25H16Cl2N4O2S</chem>	<chem>C25H16Cl2N4O2S</chem>
	CLOGP	CLOGP
	6.74	6.74
Structure	BIFM	BIFN
	<chem>C30H22Cl2N4O2</chem>	<chem>C22H16Cl2N4O2</chem>
	CLOGP	CLOGP
	7.28	5.51
Structure	BIFO	BIFP
	<chem>C31H28Cl2N4O2</chem>	<chem>C28H26Cl2N4O2</chem>
	CLOGP	CLOGP
	8.17	8.10
Structure	BIFQ	BIFR
	<chem>C28H24Cl2N4O2</chem>	<chem>C28H22Cl2N4O2</chem>
	CLOGP	CLOGP
	7.30	6.82

Structure	BIGM	BIGN
	$C_{30}H_{22}Cl_2N_4O_2$	$C_{22}H_{16}Cl_2N_4O_2$
	CLOGP	CLOGP
	5.62	3.85
Structure	BIGO	BIGP
	$C_{31}H_{28}Cl_2N_4O_2$	$C_{28}H_{26}Cl_2N_4O_2$
	CLOGP	CLOGP
	6.51	6.44
Structure	BIGQ	BIGR
	$C_{28}H_{24}Cl_2N_4O_2$	$C_{28}H_{22}Cl_2N_4O_2$
	CLOGP	CLOGP
	5.64	5.16
Structure	BIHA	BIHB
	$C_{27}H_{18}Cl_2N_4O_2$	$C_{27}H_{17}Cl_3N_4O_2$
	CLOGP	CLOGP
	6.17	6.95
Structure	BIHC	BIHD
	$C_{28}H_{20}Cl_2N_4O_3$	$C_{26}H_{17}Cl_2N_5O_2$
	CLOGP	CLOGP
	6.29	4.99
Structure	BIHE	BIHF
	$C_{30}H_{24}Cl_2N_4O_5$	$C_{27}H_{16}Cl_4N_4O_2$
	CLOGP	CLOGP
	5.52	7.68

Structure	BIKA	BIKB
	<chem>C25H18N4O2S</chem>	<chem>C25H17ClN4O2S</chem>
	CLOGP	CLOGP
	5.20	5.98
Structure	BIKC	BIKD
	<chem>C26H20N4O3S</chem>	<chem>C24H17N5O2S</chem>
	CLOGP	CLOGP
	5.32	4.02
Structure	BIKE	BIKF
	<chem>C28H24N4O5S</chem>	<chem>C25H16Cl2N4O2S</chem>
	CLOGP	CLOGP
	4.55	6.71
Structure	BIKG	BIKH
	<chem>C25H16Cl2N4O2S</chem>	<chem>C25H16Cl2N4O2S</chem>
	CLOGP	CLOGP
	5.05	5.88
Structure	BIKI	BIKJ
	<chem>C25H24N4O2S</chem>	<chem>C24H22N4O2S</chem>
	CLOGP	CLOGP
	5.74	5.19
Structure	BIKK	BIKL
	<chem>C23H16N4O2S2</chem>	<chem>C23H16N4O2S2</chem>
	CLOGP	CLOGP
	4.04	4.94

<p>Structure</p> <p>BILG</p> <p>C₂₅H₁₆Cl₂N₄O₂S</p> <p>CLOGP 5.05</p>	<p>Structure</p> <p>BILH</p> <p>C₂₅H₁₆Cl₂N₄O₂S</p> <p>CLOGP 5.88</p>
<p>Structure</p> <p>BILI</p> <p>C₂₅H₂₄N₄O₂S</p> <p>CLOGP 5.74</p>	<p>Structure</p> <p>BILJ</p> <p>C₂₄H₂₂N₄O₂S</p> <p>CLOGP 5.19</p>
<p>Structure</p> <p>BILK</p> <p>C₂₃H₁₆N₄O₂S₂</p> <p>CLOGP 4.94</p>	<p>Structure</p> <p>BILL</p> <p>C₂₃H₁₆N₄O₂S₂</p> <p>CLOGP 4.94</p>
<p>Structure</p> <p>BILM</p> <p>C₂₈H₂₂N₄O₂S</p> <p>CLOGP 5.48</p>	<p>Structure</p> <p>BILN</p> <p>C₂₀H₁₆N₄O₂S</p> <p>CLOGP 3.71</p>
<p>Structure</p> <p>BILO</p> <p>C₂₉H₂₈N₄O₂S</p> <p>CLOGP 6.37</p>	<p>Structure</p> <p>BILP</p> <p>C₂₆H₂₆N₄O₂S</p> <p>CLOGP 6.30</p>
<p>Structure</p> <p>BILQ</p> <p>C₂₆H₂₄N₄O₂S</p> <p>CLOGP 5.50</p>	<p>Structure</p> <p>BILR</p> <p>C₂₆H₂₂N₄O₂S</p> <p>CLOGP 5.02</p>



Structure		BIPG
		<chem>C28H26Cl2N4O2</chem>
		CLOGP 6.41
Structure		BIPH
		<chem>C28H26Cl2N4O2</chem>
		CLOGP 7.24
Structure		BIPK
		<chem>C26H26N4O2S</chem>
		CLOGP 6.30
Structure		BIPL
		<chem>C26H26N4O2S</chem>
		CLOGP 6.30
Structure		BIPA
		<chem>C28H28N4O2</chem>
		CLOGP 6.57
Structure		BIPB
		<chem>C28H27ClN4O2</chem>
		CLOGP 7.34
Structure		BIPC
		<chem>C29H30N4O3</chem>
		CLOGP 6.68
Structure		BIPD
		<chem>C27H27N5O2</chem>
		CLOGP 5.38
Structure		BIPE
		<chem>C31H34N4O5</chem>
		CLOGP 5.92
Structure		BIPF
		<chem>C28H26Cl2N4O2</chem>
		CLOGP 8.07

Structure	BIRK
	C ₂₆ H ₂₂ N ₄ O ₂ S
	CLOGP
	5.02

Structure	BIRL
	C ₂₆ H ₂₂ N ₄ O ₂ S
	CLOGP
	5.02

Structure	BIRG
	C ₂₈ H ₂₂ Cl ₂ N ₄ O ₂
	CLOGP
	5.12

Structure	BIRH
	C ₂₈ H ₂₂ Cl ₂ N ₄ O ₂
	CLOGP
	5.95

Structure	BIRA
	C ₂₈ H ₂₄ N ₄ O ₂
	CLOGP
	5.28

Structure	BIRB
	C ₂₈ H ₂₃ ClN ₄ O ₂
	CLOGP
	6.05

Structure	BIRC
	C ₂₉ H ₂₆ N ₄ O ₃
	CLOGP
	5.39

Structure	BIRD
	C ₂₇ H ₂₃ N ₅ O ₂
	CLOGP
	4.09

Structure	BIRE
	C ₃₁ H ₃₀ N ₄ O ₅
	CLOGP
	4.63

Structure	BIRF
	C ₂₈ H ₂₂ Cl ₂ N ₄ O ₂
	CLOGP
	6.78

CH₂Ph, and CH₂C₆H₄-F(p-). R₁ and R₂ are independently selected from the group consisting of H, aryl, substituted aryl, cycloaryl substituted cycloaryl, multi-ring cycloaryl, benzyl, substituted benzyl, alkyl, cycloalkyl substituted cycloalkyl, multi-ring cycloalkyl, fused-ring aliphatic, cyclopropyl, substituted cyclopropyl, cyclobutyl, substituted cyclobutyl, cyclopentyl, substituted cyclopentyl, cyclohexyl, substituted cyclohexyl, cycloheptyl, substituted cycloheptyl, bicycloheptyl, bicyclooctyl, bicyclononyl, substituted bicycloalknyl, adamantyl, substituted adamantyl and the like, wherein at least one of R1 and R2 are aromatic groups. Substitutions are alkyl, aryl, CF₃, CH₃, OCH₃, OH, CN, COOR, COOH and the like.

In a variation of the above-disclosed method, at least one additional active ingredient may be administered in conjunction with the administration of the compound. The additional active ingredient may be combined with said compound in a pharmaceutically acceptable diluent and co-administered to the mammal. The additional active ingredient may be a short-acting β₂-adrenergic agonist selected from the group consisting of terbutaline and albuterol. In a variation, the additional active ingredient may be a long-acting β₂-adrenergic agonist selected from the group consisting of salmeterol and formoterol or an antihistamine selected from the group consisting of loratadine, azelastine and ketotifen. In another variation, the additional active ingredient may be a phosphodiesterase inhibitor, an anticholinergic agent, a corticosteroid, an inflammatory mediator release inhibitor or a leukotriene receptor antagonist.

The compound is preferably administered at a dose of about 0.01 mg to about 100 mg per kg body weight per day in divided doses of said compound for at least two consecutive days at regular periodic intervals.

Other variations within the scope of the present invention may be more fully understood with reference to the following detailed description.

Detailed Description of the Preferred Embodiment

The present invention is directed to small molecule inhibitors of IgE (synthesis and/or release) which are useful in the treatment of allergy and/or asthma or any diseases where IgE is pathogenic. The particular compounds disclosed herein were identified by their ability to suppress IgE levels in both *ex vivo* and *in vivo* assays. Development and optimization of clinical treatment regimens can be monitored by those of skill in the art by reference to the *ex vivo* and *in vivo* assays described below.

antibody was about 200-400 pg/ml and there was less than 0.001% cross-reactivity with any other Ig isotype in the ELISA for IgE.

In Vivo Assay

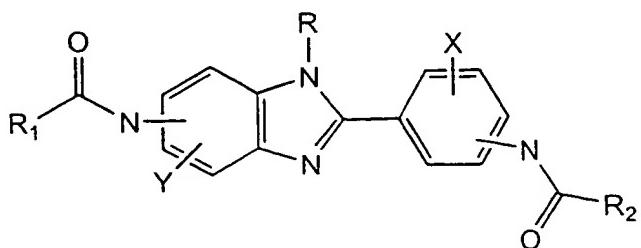
Compounds found to be active in the *ex vivo* assay (above) were further tested for their activity in suppressing IgE responses *in vivo*. Mice receiving low-dose radiation prior to immunization with a carrier exhibited an enhanced IgE response to sensitization with antigen 7 days later. Administration of the test compounds immediately prior to and after antigen sensitization, measured the ability of that drug to suppress the IgE response. The levels of IgE, IgG1 and IgG2a in serum were compared.

Female BALB/cByj mice were irradiated with 250 rads 7 hours after initiation of the daily light cycle. Two hours later, the mice were immunized i.p. with 2 µg of KLH in 4 mg alum. Two to seven consecutive days of drug injections were initiated 6 days later on either a once or twice daily basis. Typically, i.p. injections and oral gavages were administered as suspensions (150 µl/injection) in saline with 10% ethanol and 0.25% methylcellulose. Each treatment group was composed of 5-6 mice. On the second day of drug administration, 2 µg of DNP-KLH was administered i.p. in 4 mg alum, immediately following the morning injection of drug. Mice were bled 7-21 days following DNP-KLH challenge.

Antigen-specific IgE, IgG1 and IgG2a antibodies were measured by ELISA. Periorbital bleeds were centrifuged at 14,000 rpm for 10 min, the supernatants were diluted 5-fold in saline, and centrifuged again. Antibody concentrations of each bleed were determined by ELISA of four dilutions (in triplicate) and compared to a standard curve: anti-DNP IgE (1:100 to 1:800), anti-DNP IgG2a (1:100 to 1:800), and anti-DNP IgG1 (1:1600 to 1:12800).

Diacyl Benzimidazole Inhibitors of IgE

Several species embraced by the following generic formula were synthesized and evaluated for their effectiveness in down-regulating IgE in the *ex vivo* and *in vivo* assays.



filtered and washed with copious amounts of water. The residue was then dried to obtain 16.9 g of crude desired product. Mass spectrum analysis (positive ion) indicated presence of 3.

Synthesis of 4: Benzimidazole 3 (800 mg, 3.14 mmol) was dissolved in dry pyridine (5 ml) in a scintillation vial and the desired acid chlorides (1.1 eq) were added slowly. The reactions were carried out in an oven at 60C. After 16h, the reaction was cooled to RT and DI water was added. Precipitation took place, which was filtered off, washed with water and air dried. The aqueous layer was extracted with EtOAc (6 x 50 ml), dried over anhydrous Na₂SO₄ and the solvent was removed *in vacuo* to result in a colored solid. By positive ion MS the desired monoacylated product was found to be present in the initial precipitate as well as in the organic layer. Hence the solid residues obtained were combined and used as such for the reduction step.

Reduction of 4: Crude monoacylated nitro benzimidazole 4 (1.22 g, 3.40 mmol) was dissolved in MeOH (20 ml) and minimum amount of THF was added for complete dissolution to occur. Catalytic amount of 10% Pd on C was added and the solution was degassed and allowed to stir at 3.4 atm pressure under H₂ atmosphere for 4 h. Upon completion of reaction as observed via TLC, the reaction mixture was filtered through celite and the solvent was removed under reduced pressure to afford 979 mg of crude residue.

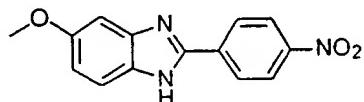
General Organic Analyses

HPLC/MS data was obtained using a Gilson semi-prep HPLC with a Gilson 170 Diode Array UV detector and PE Sciex API 100LC MS based detector. A Waters 600E with a Waters 490E UV detector was also used for recording HPLC data. The compounds were eluted with a gradient of CH₃CN (with 0.0035% TFA) and H₂O (with 0.01% TFA). Both HPLC instruments used Advantage C18 60A 5μ 50mm x 4.6mm columns from Thomson Instrument Company. Mass spectra were obtained by direct injection and electrospray ionization on a PE Sciex API 100LC MS based detector. Thin layer chromatography was performed using Merck 60F-254 aluminum backed precoated plates. Flash chromatography was carried out on Merck silica gel 60 (230-400 mesh) purchased from EM Scientific.

Syntheses of Symmetrical Diamides

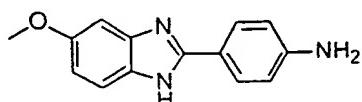
of the desired product was precipitated by the addition of ethanol. The resulting solid was filtered, re-dissolved in water and the solution made basic by the addition of concentrated ammonium hydroxide. The resulting precipitate was filtered and dried overnight under vacuum to yield the desired product as a gray solid (6.023 g, 26.9 mmole, 87%). The product characterized by electrospray mass spectroscopy and HPLC (mp. 222-227° C).

2-(4-Aminophenyl)-5-methoxy benzimidazole was synthesized from 2-(4-nitrophenyl)-5-methoxy benzimidazole, which was prepared as follows: 1,2-diamino-4-methoxybenzene (1.26 g, 10.0 mmole) was mixed with 4-nitrobenzoic acid (1.67 g, 9.8 mmole) and dissolved in POCl_3 (10 ml) and heated to reflux for 2.5 hours. The reaction mixture was cooled and cautiously poured onto ice. The resulting solid was filtered, washed with NaHCO_3 and used without further purification.



2-(4-nitrophenyl)-5-methoxy benzimidazole

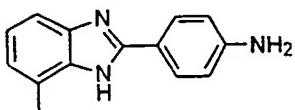
2-(4-Aminophenyl)-5-methoxy benzimidazole was prepared by dissolving 1 g of the above nitrobenzimidazole in 30% $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$ (20 ml) with stirring at RT for 21 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were dried over sodium sulfate and concentrated under vacuum. The product was characterized by mass spectroscopy.



2-(4-aminophenyl)-5-methoxy benzimidazole

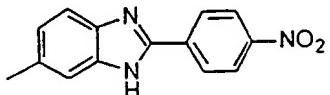
2-(4-Aminophenyl)-5,6-dichloro benzimidazole was synthesized from 2-(4-nitrophenyl)-5,6-dichloro benzimidazole, which was prepared as follows: 1,2-diamino-4,5-dichlorobenzene (1.68 g, 10.0 mmole) was mixed with 4-nitrobenzoic acid (1.58 g, 9.3 mmole), dissolved in POCl_3 (10 ml), and heated to reflux for 2.5 hours. The reaction mixture was cooled and

dried over sodium sulfate and concentrated under vacuum. The product was characterized by mass spectroscopy.



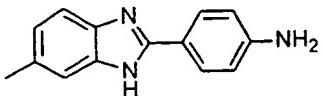
2-(4-aminophenyl)-7-methyl benzimidazole

2-(4-Aminophenyl)-6-methyl benzimidazole was synthesized from 2-(4-nitrophenyl)-6-methyl benzimidazole, which was prepared by mixing 1,2-diamino-4-methylbenzene (1.24 g, 9.8 mmole) with 4-nitrobenzoic acid (1.6 g, 9.9 mmole) and dissolved in POCl_3 (10 ml) and heated to reflux for 2.5 hours. The reaction mixture was cooled and cautiously poured onto ice. The resulting solid was filtered, washed with NaHCO_3 and used without further purification.



2-(4-nitrophenyl)-6-methyl benzimidazole

2-(4-Aminophenyl)-6-methyl benzimidazole was synthesized by dissolving 1 g of the above nitrobenzimidazole in 30% $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$ (20 ml) with stirring at RT for 4.5 h. The reaction mixture was diluted with water and extracted with EtOAc . The combined organic extracts were dried over sodium sulfate and concentrated under vacuum. The product was characterized by mass spectroscopy.



2-(4-aminophenyl)-6-methyl benzimidazole

2-(4-Aminophenyl)-5,6-dimethyl benzimidazole was synthesized from 2-(4-nitrophenyl)-5,6-dimethyl benzimidazole, which was prepared by mixing 1,2-diamino-4,5-dimethylbenzene (1.38 g, 10.1 mmole) with 4-nitrobenzoic acid (1.69 g, 9.9 mmole) and dissolved in POCl_3 (10 ml) and heated to reflux for 2.5 hours. The reaction mixture was cooled and cautiously poured

being washed by hexanes and water and NaHCO₃ (aq.). The resulting residue was purified on silica gel (hexanes/EtOAc or MeOH/CH₂Cl₂) or reverse phase HPLC (CH₃CN/H₂O).

Method C: 2-(4-Aminophenyl)-6-aminobenzimidazole (1 mmole) was suspended in THF (10 ml) to which was added K₂CO₃ (2.5 mmole) in water (0.5 ml), and mixture cooled to -78° C. To the above cooled mixture was added the acid chloride (2.5 mmole) and let warm to RT overnight. Water (10 ml) was added to the reaction and extracted with EtOAc. The combined organic extracts were combined washed with NaHCO₃ (aq.) and concentrated under reduced pressure. The resulting residue was purified on silica gel (hexanes/EtOAc or MeOH/CH₂Cl₂) or reverse phase HPLC (CH₃CN/H₂O).

Method D: The carboxylic acid (2.2 mmole), EDC (2.2 mmole) and DMAP (cat.) was dissolved in hot pyridine. To the above solution was added 2-(4-aminophenyl)-6-aminobenzimidazole (1 mmole) and heated to 60° C overnight. The cooled reaction mixture was partitioned between water and EtOAc. The organic layer was washed with NaHCO₃, dried over Na₂SO₄ and concentrated under vacuum. The resulting residue was purified on silica gel (hexanes/EtOAc or MeOH/CH₂Cl₂) or reverse phase HPLC (CH₃CN/H₂O).

Diacyl Benzimidazole Species

The following species encompassed within the disclosed generic formula were synthesized and tested for their ability to suppress IgE. The species are presented *above in the Summary of the Invention*

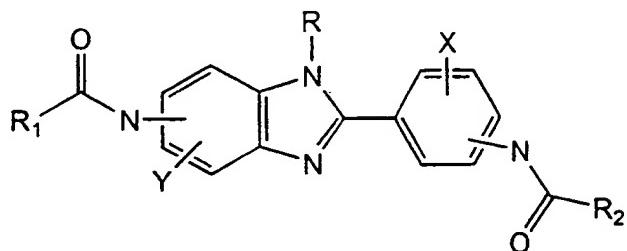
for example Hasegawa et al., *J. Med. Chem.* 40: 395-407 (1997) and Ohmori et al., *Int. J. Immunopharmacol.* 15:573-579 (1993); employing similar *ex vivo* and *in vivo* assays for determining dose-response relationships for IgE suppression by naphthalene derivatives; incorporated herein by reference).

Initially, suitable dosages of the compounds will generally range from about 0.001 mg to about 300 mg per kg body weight per day in divided doses, more preferably, between about 0.01 mg and 100 mg per kg body weight per day in divided doses. The compounds are preferably administered systemically as pharmaceutical formulations appropriate to such routes as oral, aerosol, intravenous, subcutaneously, or by any other route which may be effective in providing systemic dosing of the active compound. The compositions of pharmaceutical formulations are well known in the art. The treatment regimen preferably involves periodic administration. Moreover, long-term therapy may be indicated where allergic reactions appear to be triggered by continuous exposure to the allergen(s). Daily or twice daily administration has been effective in suppressing the IgE response to a single antigen challenge in animals when carried out continuously from a period of two to seven consecutive days. Thus, in a preferred embodiment, the compound is administered for at least two consecutive days at regular periodic intervals. However, the treatment regimen, including frequency of dosing and duration of treatment may be determined by the skilled practitioner, and modified as needed to provide optimal IgE down-regulation, depending on nature of the allergen, the dose, frequency, and duration of the allergen exposure, and the standard clinical indices.

In one embodiment of the present invention, an IgE-suppressing compound may be administered in conjunction with one or more of the other small molecule inhibitors disclosed, in order to produce optimal down-regulation of the patient's IgE response. Further, it is envisioned that one or more of the compounds of the present invention may be administered in combination with other drugs already known or later discovered for treatment of the underlying cause as well as the acute symptoms of allergy or asthma. Such combination therapies envisioned within the scope of the present invention include mixing of one or more of the small molecule IgE-inhibitors together with one or more additional ingredients, known to be effective in reducing at least one symptom of the disease condition. In a variation, the small molecule IgE-inhibitors herein disclosed may be administered separately from the additional drugs, but during the same course of the disease

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising the following compounds:



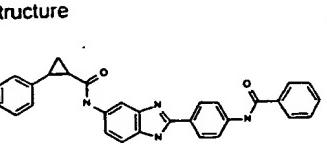
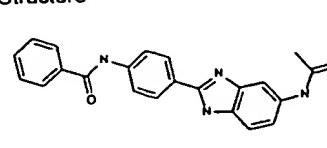
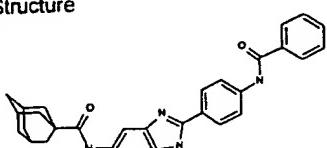
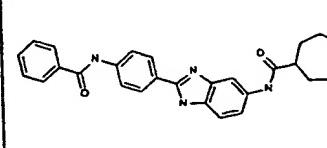
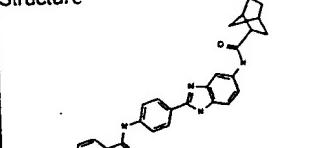
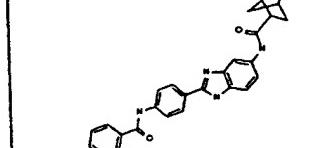
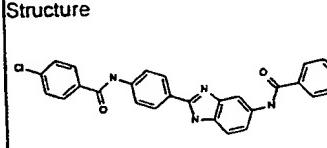
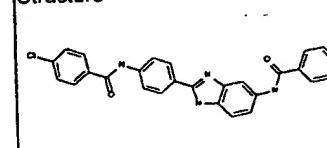
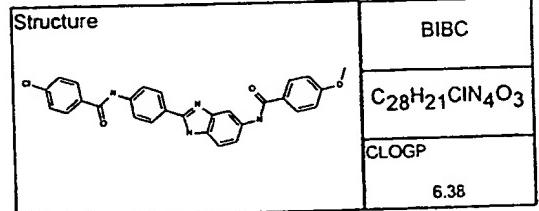
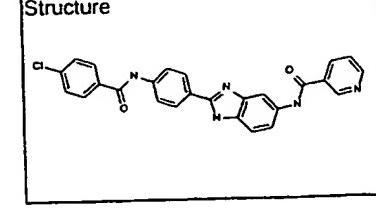
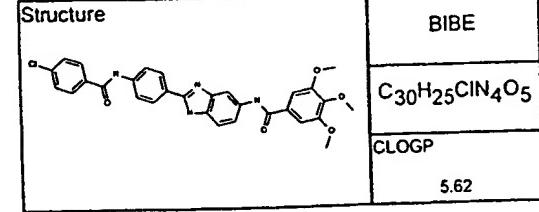
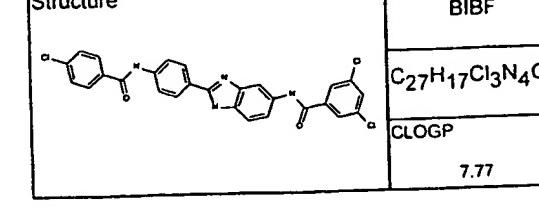
wherein X and Y are independently selected from the group consisting of H, alkyl, alkoxy, aryl, substituted aryl, hydroxy, halogen, amino, alkylamino, nitro, cyano, CF_3 , OCF_3 , $CONH_2$, $CONHR$ and $NHCOR_1$;

wherein R is selected from the group consisting of H, CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , CH_2Ph , and $CH_2C_6H_4-F(p-)$; and

wherein R_1 and R_2 are independently selected from the group consisting of H, aryl, substituted aryl, cycloaryl substituted cycloaryl, multi-ring cycloaryl, benzyl, substituted benzyl, alkyl, cycloalkyl substituted cycloalkyl, multi-ring cycloalkyl, fused-ring aliphatic, cyclopropyl, substituted cyclopropyl, cyclobutyl, substituted cyclobutyl, cyclopentyl, substituted cyclopentyl, cyclohexyl, substituted cyclohexyl, cycloheptyl, substituted cycloheptyl, bicycloheptyl, bicyclooctyl, bicyclononyl, substituted bicycloalknyl, adamantyl, substituted adamantyl and the like, wherein at least one of R_1 and R_2 are aromatic groups.

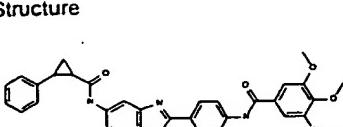
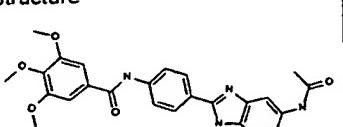
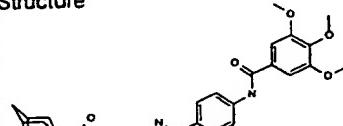
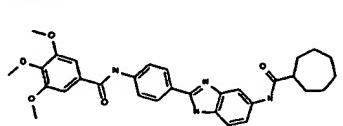
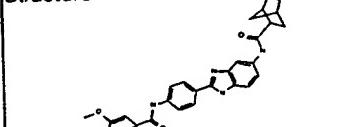
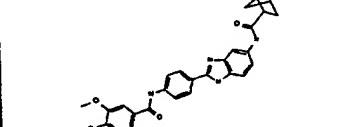
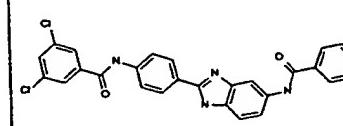
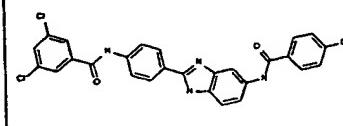
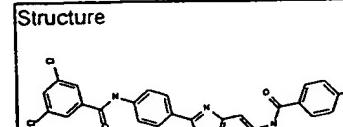
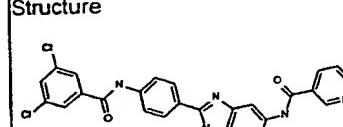
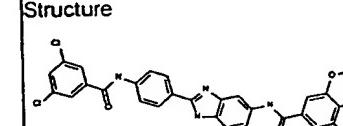
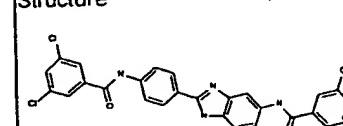
2. The pharmaceutical composition of claim 1, wherein the R_1 and R_2 substitutions are selected from the group consisting of alkyl, aryl, CF_3 , CH_3 , OCH_3 , OH, CN, $COOR$ and $COOH$.

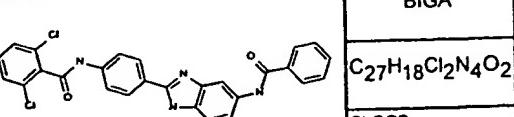
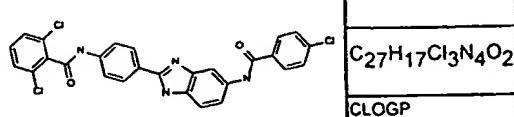
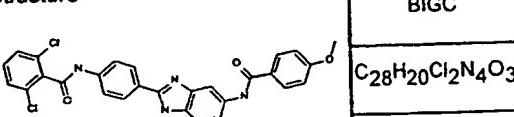
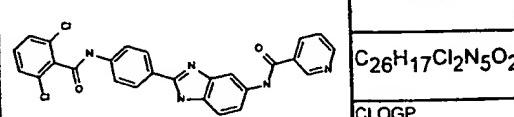
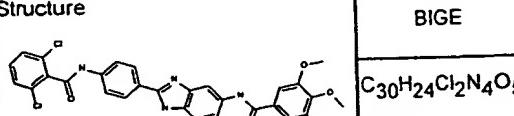
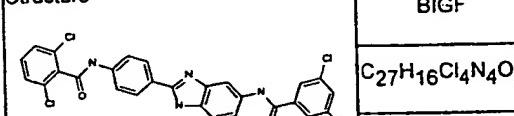
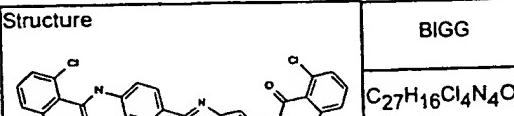
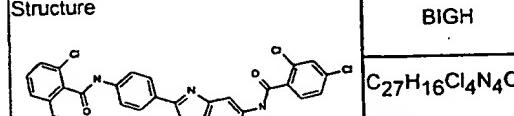
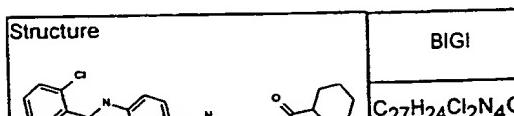
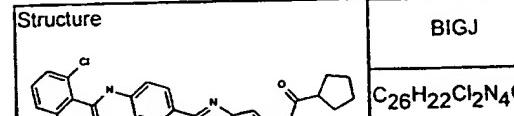
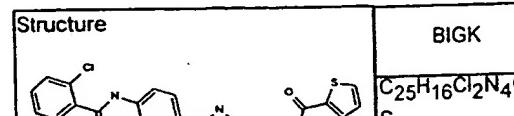
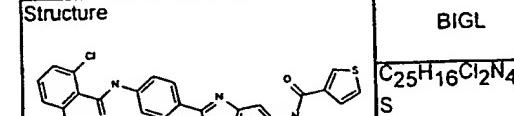
3. The pharmaceutical composition of Claim 2, wherein the compound is selected from the group consisting of:

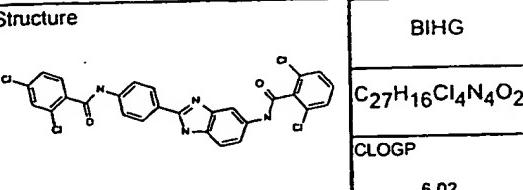
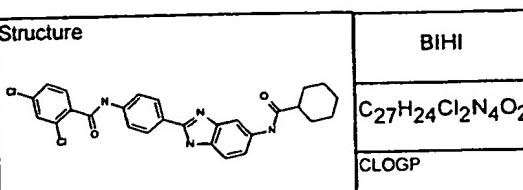
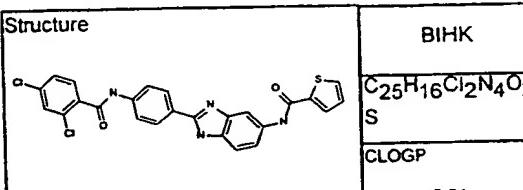
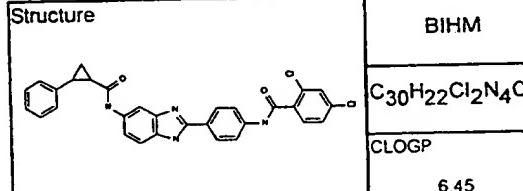
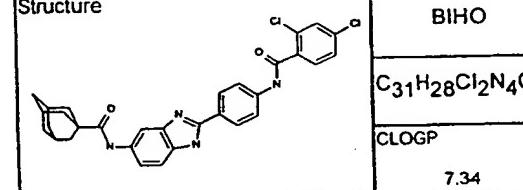
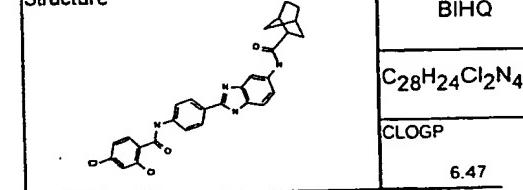
Structure		BIAM
		$C_{30}H_{24}N_4O_2$
		CLOGP 5.74
Structure		BIAN
		$C_{22}H_{18}N_4O_2$
		CLOGP 3.98
Structure		BIAO
		$C_{31}H_{30}N_4O_2$
		CLOGP 6.64
Structure		BIAP
		$C_{28}H_{28}N_4O_2$
		CLOGP 6.57
Structure		BIAQ
		$C_{28}H_{26}N_4O_2$
		CLOGP 5.76
Structure		BIAR
		$C_{28}H_{24}N_4O_2$
		CLOGP 5.28
Structure		BIBA
		$C_{27}H_{19}ClN_4O_2$
		CLOGP 6.26
Structure		BIBB
		$C_{27}H_{18}Cl_2N_4O_2$
		CLOGP 7.04
Structure		BIBC
		$C_{28}H_{21}ClN_4O_3$
		CLOGP 6.38
Structure		BIBD
		$C_{26}H_{18}ClN_5O_2$
		CLOGP 5.08
Structure		BIBE
		$C_{30}H_{25}ClN_4O_5$
		CLOGP 5.62
Structure		BIBF
		$C_{27}H_{17}Cl_3N_4O_2$
		CLOGP 7.77

Structure	BICA	Structure	BICB
	$C_{28}H_{22}N_4O_3$		$C_{28}H_{21}ClN_4O_3$
	CLOGP 5.58		CLOGP 6.35
Structure	BICC	Structure	BICD
	$C_{29}H_{24}N_4O_4$		$C_{27}H_{21}N_5O_3$
	CLOGP 5.70		CLOGP 4.39
Structure	BICE	Structure	BICF
	$C_{31}H_{28}N_4O_6$		$C_{28}H_{20}Cl_2N_4O_3$
	CLOGP 4.93		CLOGP 7.09
Structure	BICG	Structure	BICH
	$C_{28}H_{20}Cl_2N_4O_3$		$C_{28}H_{20}Cl_2N_4O_3$
	CLOGP 5.43		CLOGP 6.26
Structure	BICI	Structure	BICJ
	$C_{28}H_{28}N_4O_3$		$C_{27}H_{26}N_4O_3$
	CLOGP 6.12		CLOGP 5.56
Structure	BICK	Structure	BICL
	$C_{26}H_{20}N_4O_3S$		$C_{26}H_{20}N_4O_3S$
	CLOGP 5.32		CLOGP 5.32

Structure	BIDG	BIDH
	<chem>C26H17Cl2N5O2</chem>	<chem>C26H17Cl2N5O2</chem>
	CLOGP	CLOGP
	4.44	5.27
Structure	BIDI	BIDJ
	<chem>C26H25N5O2</chem>	<chem>C25H23N5O2</chem>
	CLOGP	CLOGP
	5.14	4.58
Structure	BIDK	BIDL
	<chem>C24H17N5O2S</chem>	<chem>C24H17N5O2S</chem>
	CLOGP	CLOGP
	4.33	4.33
Structure	BIDM	BIDN
	<chem>C29H23N5O2</chem>	<chem>C21H17N5O2</chem>
	CLOGP	CLOGP
	4.87	3.11
Structure	BIDO	BIDP
	<chem>C30H29N5O2</chem>	<chem>C27H27N5O2</chem>
	CLOGP	CLOGP
	5.77	5.70
Structure	BIDQ	BIDR
	<chem>C27H25N5O2</chem>	<chem>C27H23N5O2</chem>
	CLOGP	CLOGP
	4.89	4.41

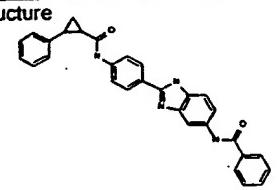
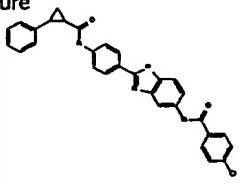
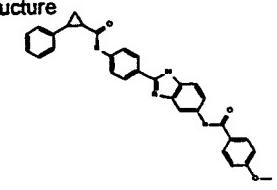
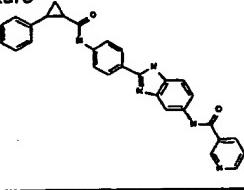
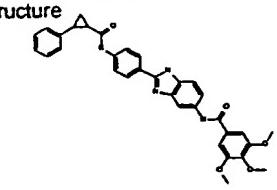
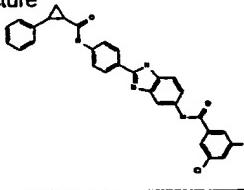
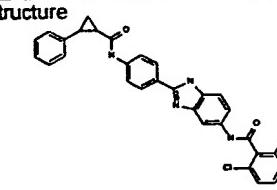
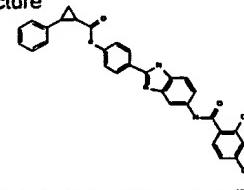
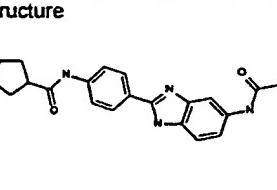
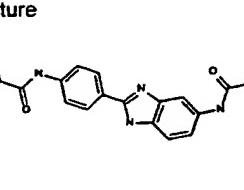
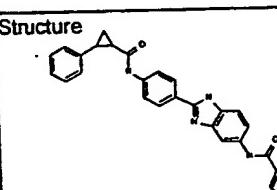
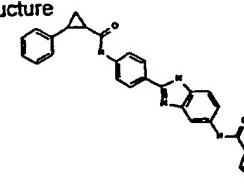
Structure	BIEM	BIEN	
	C ₃₃ H ₃₀ N ₄ O ₅ CLOGP 5.09		C ₂₅ H ₂₄ N ₄ O ₅ CLOGP 3.33
Structure	BIEO	BIEP	
	C ₃₄ H ₃₆ N ₄ O ₅ CLOGP 5.99		C ₃₁ H ₃₄ N ₄ O ₅ CLOGP 5.92
Structure	BIEQ	BIER	
	C ₃₁ H ₃₂ N ₄ O ₅ CLOGP 5.11		C ₃₁ H ₃₀ N ₄ O ₅ CLOGP 4.63
Structure	BIFA	BIFB	
	C ₂₇ H ₁₈ Cl ₂ N ₄ O ₂ CLOGP 7.00		C ₂₇ H ₁₇ Cl ₃ N ₄ O ₂ CLOGP 7.78
Structure	BIFC	BIFD	
	C ₂₈ H ₂₀ Cl ₂ N ₄ O ₃ CLOGP 7.12		C ₂₆ H ₁₇ Cl ₂ N ₅ O ₂ CLOGP 5.82
Structure	BIFE	BIFF	
	C ₃₀ H ₂₄ Cl ₂ N ₄ O ₅ CLOGP 6.35		C ₂₇ H ₁₆ Cl ₄ N ₄ O ₂ CLOGP 8.51

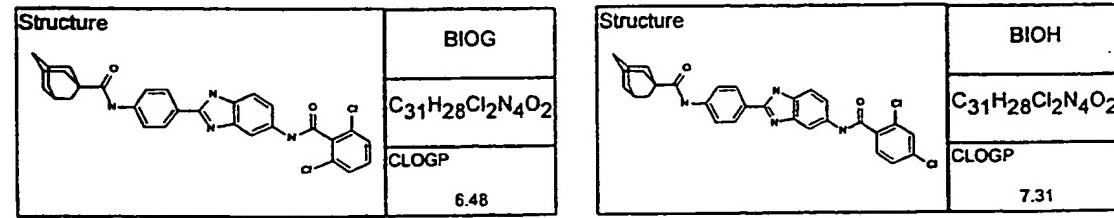
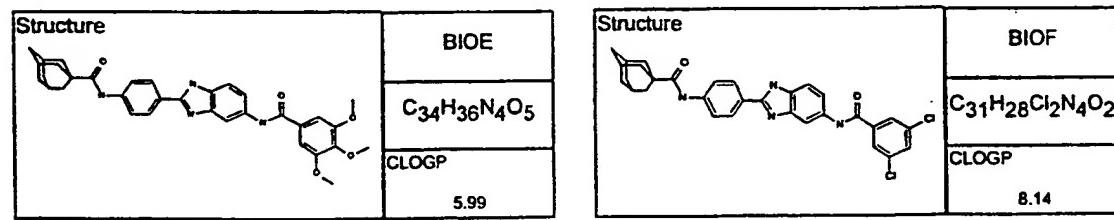
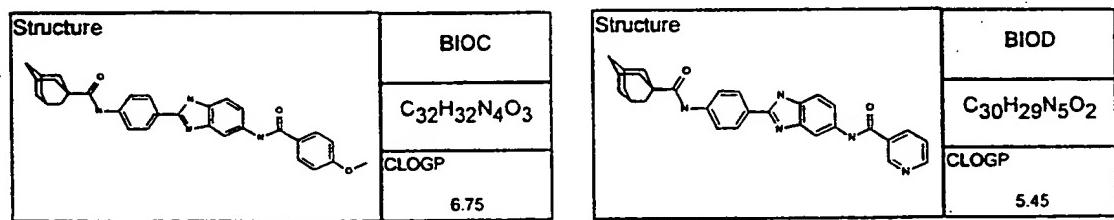
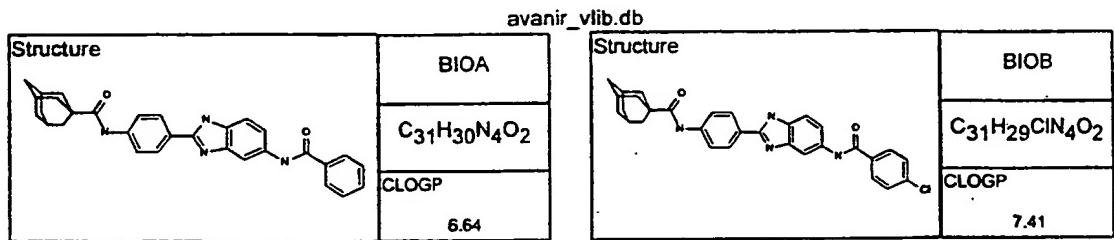
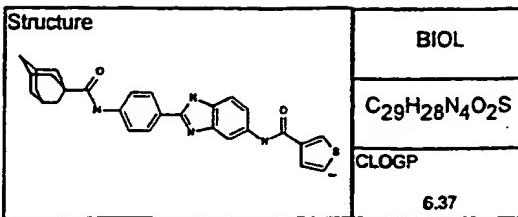
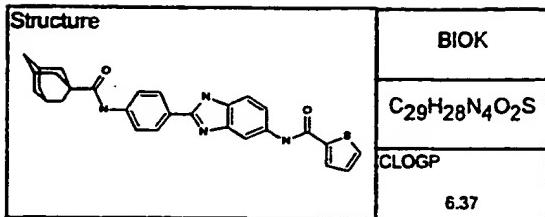
Structure	BIGA	Structure	BIGB
	<chem>C27H18Cl2N4O2</chem>		<chem>C27H17Cl3N4O2</chem>
	CLOGP 5.34		CLOGP 6.12
Structure	BIGC	Structure	BIGD
	<chem>C28H20Cl2N4O3</chem>		<chem>C26H17Cl2N5O2</chem>
	CLOGP 5.46		CLOGP 4.16
Structure	BIGE	Structure	BIGF
	<chem>C30H24Cl2N4O5</chem>		<chem>C27H16Cl4N4O2</chem>
	CLOGP 4.69		CLOGP 6.85
Structure	BIGG	Structure	BIGH
	<chem>C27H16Cl4N4O2</chem>		<chem>C27H16Cl4N4O2</chem>
	CLOGP 5.19		CLOGP 6.02
Structure	BIGI	Structure	BIGJ
	<chem>C27H24Cl2N4O2</chem>		<chem>C26H22Cl2N4O2</chem>
	CLOGP 5.88		CLOGP 5.33
Structure	BIGK	Structure	BIGL
	<chem>C25H16Cl2N4O2</chem> S		<chem>C25H16Cl2N4O2</chem> S
	CLOGP 5.08		CLOGP 5.08

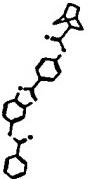
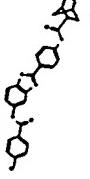
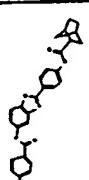
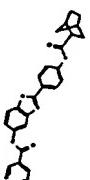
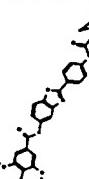
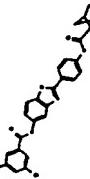
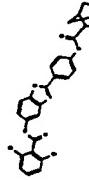
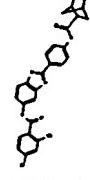
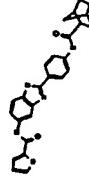
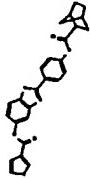
Structure	BIHG	BIHH
	<chem>C27H16Cl4N4O2</chem>	<chem>C27H16Cl4N4O2</chem>
	CLOGP	CLOGP
	6.02	6.85
Structure	BIHI	BIHJ
	<chem>C27H24Cl2N4O2</chem>	<chem>C26H22Cl2N4O2</chem>
	CLOGP	CLOGP
	6.71	6.16
Structure	BIHK	BIHL
	<chem>C25H16Cl2N4O2S</chem>	<chem>C25H16Cl2N4O2S</chem>
	CLOGP	CLOGP
	5.91	5.91
Structure	BIHM	BIHN
	<chem>C30H22Cl2N4O2</chem>	<chem>C22H16Cl2N4O2</chem>
	CLOGP	CLOGP
	6.45	4.68
Structure	BIHO	BIHP
	<chem>C31H28Cl2N4O2</chem>	<chem>C28H26Cl2N4O2</chem>
	CLOGP	CLOGP
	7.34	7.27
Structure	BIHQ	BIHR
	<chem>C28H24Cl2N4O2</chem>	<chem>C28H22Cl2N4O2</chem>
	CLOGP	CLOGP
	6.47	5.99

Structure	BIKM	BIKN
	<chem>C28H22N4O2S</chem>	<chem>C20H16N4O2S</chem>
	CLOGP 5.48	CLOGP 3.71
Structure	BIKO	BIKP
	<chem>C29H28N4O2S</chem>	<chem>C26H26N4O2S</chem>
	CLOGP 6.37	CLOGP 6.30
Structure	BIKQ	BIKR
	<chem>C26H24N4O2S</chem>	<chem>C26H22N4O2S</chem>
	CLOGP 5.50	CLOGP 5.02
Structure	BILA	BILB
	<chem>C25H18N4O2S</chem>	<chem>C25H17ClN4O2S</chem>
	CLOGP 5.20	CLOGP 5.98
Structure	BILC	BILD
	<chem>C26H20N4O3S</chem>	<chem>C24H17N5O2S</chem>
	CLOGP 5.32	CLOGP 4.02
Structure	BILE	BILF
	<chem>C28H24N4O5S</chem>	<chem>C25H16Cl2N4O2S</chem>
	CLOGP 4.55	CLOGP 6.71

Structure	BIJG	BIJH
	C ₂₆ H ₂₂ Cl ₂ N ₄ O ₂ CLOGP 5.29	C ₂₆ H ₂₂ Cl ₂ N ₄ O ₂ CLOGP 6.12
Structure	BIIA	BIIB
	C ₂₇ H ₂₆ N ₄ O ₂ CLOGP 6.01	C ₂₇ H ₂₅ ClN ₄ O ₂ CLOGP 6.78
Structure	BIIC	BIID
	C ₂₈ H ₂₈ N ₄ O ₃ CLOGP 6.12	C ₂₆ H ₂₅ N ₅ O ₂ CLOGP 4.82
Structure	BIIE	BIIF
	C ₃₀ H ₃₂ N ₄ O ₅ CLOGP 5.36	C ₂₇ H ₂₄ Cl ₂ N ₄ O ₂ CLOGP 7.51
Structure	BIIG	BIIH
	C ₂₇ H ₂₄ Cl ₂ N ₄ O ₂ CLOGP 5.85	C ₂₇ H ₂₄ Cl ₂ N ₄ O ₂ CLOGP 6.68

Structure		BIMA
		<chem>C30H24N4O2</chem>
		CLOGP 5.74
Structure		BIMB
		<chem>C30H23ClN4O2</chem>
		CLOGP 6.51
Structure		BIMC
		<chem>C31H26N4O3</chem>
		CLOGP 5.85
Structure		BIMD
		<chem>C29H23N5O2</chem>
		CLOGP 4.55
Structure		BIME
		<chem>C33H30N4O5</chem>
		CLOGP 5.09
Structure		BIMF
		<chem>C30H22Cl2N4O2</chem>
		CLOGP 7.24
Structure		BIMG
		<chem>C30H22Cl2N4O2</chem>
		CLOGP 5.58
Structure		BIMH
		<chem>C30H22Cl2N4O2</chem>
		CLOGP 6.41
Structure		BIJK
		<chem>C24H22N4O2S</chem>
		CLOGP 5.19
Structure		BIJL
		<chem>C24H22N4O2S</chem>
		CLOGP 5.19
Structure		BIMK
		<chem>C28H22N4O2S</chem>
		CLOGP 5.48
Structure		BIML
		<chem>C28H22N4O2S</chem>
		CLOGP 5.48



Structure	BIQA
	<chem>C28H26N4O2</chem>
CLOGP	5.76
Structure	BIQB
	<chem>C28H25ClN4O2</chem>
CLOGP	6.54
Structure	BIQC
	<chem>C29H28N4O3</chem>
CLOGP	5.88
Structure	BIQD
	<chem>C27H25N5O2</chem>
CLOGP	4.57
Structure	BIQE
	<chem>C31H32N4O5</chem>
CLOGP	5.11
Structure	BIQF
	<chem>C28H24Cl2N4O2</chem>
CLOGP	7.27
Structure	BIQG
	<chem>C28H24Cl2N4O2</chem>
CLOGP	5.61
Structure	BIQH
	<chem>C28H24Cl2N4O2</chem>
CLOGP	6.44
Structure	BIQK
	<chem>C26H24N4O2S</chem>
CLOGP	5.50
Structure	BIQL
	<chem>C26H24N4O2S</chem>
CLOGP	5.50

4. The pharmaceutical composition of any of Claims 1-3 for use in the treatment of a disease condition associated with excess IgE.

5. The pharmaceutical composition of Claim 4, further comprising at least one additional ingredient which is active in reducing at least one symptom associated with the disease condition associated with excess IgE.

6. The pharmaceutical composition of Claim 5, wherein said at least one additional ingredient is selected from the group consisting of a short-acting β_2 -adrenergic agonist, a long-acting β_2 -adrenergic agonist, an antihistamine, a phosphodiesterase inhibitor, an anticholinergic agent, a corticosteroid, an inflammatory mediator release inhibitor and a leukotriene receptor antagonist.

7. Use of the pharmaceutical composition of any one of Claims 1-3 in the preparation of a medicament for treatment of a disease condition associated with excess IgE.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/11322

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION SHEET PCT/ISA/210

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/11322

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 0719765 A	03-07-1996	JP 8231514 A		10-09-1996